UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/893,499	06/29/2001	J. Norman Hansen	108172-00056	6341

4372 7590 11/03/2004

ARENT FOX KINTNER PLOTKIN & KAHN
1050 CONNECTICUT AVENUE, N.W.
SUITE 400
WASHINGTON, DC 20036

EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/893,499	HANSEN, J. NORMAN	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/29/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-10 are currently pending.

Claims 1-9 are under consideration.

Claim 10 is withdrawn from consideration as being directed to a nonelected invention.

Election/Restriction

1. Applicant's election of Group I (claims 1-9) in the correspondence dated 5/28/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claim 10 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

2. Applicant's further election of: an antibody (as a target species) and modifying enzymatic activity of an enzyme (as species of biological activity change) in the correspondence dated 8/30/04 in response to the election of species is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Information Disclosure Statement

3. Listing references in the specification (e.g. pages 25-26) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1 (and claims dependent thereon) the metes and bounds of amino acids that constitute "a subtilin leader *segment*" is unclear. The specification (e.g. on page 8) defines "a subtilin leader *peptide*" as being amino acids 58-81 of seq. Id 2 ("residues 78-81 are necessary"); whereas the specification on page 9 refers to "a subtilin leader segment" functionally (e.g. "it retain its affinity for the cell wall") and not structurally. Accordingly, it is unclear as to whether "a subtilin leader segment" comprises amino acids constituting the "subtilin leader peptide" or a portion thereof ;or amino acids partially or totally unrelated thereto.

B. In claim 3, "the nucleophilic group" lacks clear antecedent basis.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (e.g. lack of written description).

The presently claimed invention is directed to methods of:

I. Detecting binding of a target molecule to a "Lantibody display Peptide" by reacting a **"host cell"** expressing the lantibody display peptide on its surface with the target molecule and measuring a change in biological activity of the target molecule (claim 1); or

II. Screening a "Lantibody display library" for binding to one or more target molecules by reacting a "plurality of *bacterial cells*" expressing different lantibody display peptides on their surfaces, with one or more target molecules and isolating bacterial cells binding a target molecule "using means for recognizing the binding agent" (claim 7).

The above methods employ the use of chimeric lantibiotic display peptides that comprise:

1. A "lantibiotic peptide" (see specification pages 1-2 and definition thereof);

2. An "amino acid spacer" attached to the C-terminus of the lantibiotic peptide; and

3. A **"subtilin leader segment"** attached to the spacer. See present claim 1.

Lantibodies bind "specifically to desired molecules" in the nature of antibodies (see specification pages 2-3). However, although the specification (e.g. on pages 6-8) defines "a subtilin leader peptide" as being amino acids 58-81 of seq. Id 2, with the

presence of at least amino acid residues 78-81 of seq. Id 2 being critical (e.g. see specification at pages 6-8: "residues 78-81 are necessary"); the specification on pages 8-10 refer to "a subtilin leader segment" *functionally* (e.g. "it retain its affinity for the cell wall") and not structurally. Accordingly, "a subtilin leader segment" may comprise amino acids constituting the "subtilin leader peptide" or any portion thereof (one or more of any amino acid w/n 58-81 of seq. Id 2) or even amino acids unrelated or partially related thereto.

In support thereof the specification examples are directed to the making or use of lantibiotic display peptides directed to sublancin (as the "lantibiotic peptide") attached (via its C-terminus) to polyglycine linkers of defined length to which is attached to the subtilin leader peptide sequence (amino acids 58-81 of Seq. Id. 2) via its N-terminus.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

Although directed to DNA compounds, this holding would be deemed to be applicable to a generic of compounds; which requires a representative sample of

compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the compound or generic(s). For example, in a recent court case in line with *Eli Lilly, Judge Lourie writing for the CAFC* made the following observation:

"A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) having the function of lessening inflammation of tissues, fails to distinguish any steroid from others having the same activity or function. Similarly, the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity. "

See: J. Lourie decision in *Enzo Biochem, Inc. v. Gen-Probe Inc. et al.* No. 01-1230 (CAFC: Decided April 2, 2002) (citation forthcoming).

In this regard, applicant is further referred to the case of *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and the "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001).

It is noted that written description is legally distinct from enablement: "Although the two concepts of are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures the that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co.*

Accordingly, claiming "a subtilin leader segment" in purely function terms, without reference to any amino acid structure whatsoever lacks adequate written description. It is also noted that the first methods reference to a generic of "host cells" is not supported by the specification illustration of the critical use of specific bacterial host cells for recombinantly expressing lantibiotic chimera leader/structural peptidic regions.

8. Claims 5 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matterwhich was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (e.g. lack of written description).

The presently claimed invention is directed to methods of:

I. Detecting binding of a target molecule to a "Lantibody display Peptide" by reacting a "host cell" expressing the lantibody display peptide on its surface with the target molecule and measuring a change in biological activity of the target molecule (claim 1); or

II. Screening a "Lantibody display library" for binding to one or more target molecules by reacting a "plurality of bacterial cells" expressing different lantibody display peptides on their surfaces, with one or more target molecules and isolating bacterial cells binding a target molecule "using means for recognizing the binding agent" (claim 7).

The above methods employ the use of chimeric lantibiotic display peptides that comprise:

1. A "lantibiotic peptide" (see specification page 1 definition thereof);

2. An "amino acid spacer" attached to the C-terminus of the lantibiotic peptide; and

3. A "subtilin leader segment" attached to the spacer. See present claim 1.

Lantibodies bind "specifically to desired molecules" in the nature of antibodies (see specification pages 2-3).

Claims 5 and 9 recite that the Lantibody Display peptide comprises "sublancin 168" and "sublancin", respectively.

A name of a protein in the absence of sufficient structural information (e.g. SEQ ID. No.) or functional characteristics does not serve to identify the claimed invention. It is noted that the name of a protein or peptide can change over time, as more becomes known about the peptide/protein, e.g. the alternate known names for interleukin 1. The only example of a sublancin in the specification is that of sublancin 168 of SEQ ID 2 (e.g. 1-38 of SEQID 2 as part of the chimera).

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in

University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)].

Although directed to DNA compounds, this holding would be deemed to be applicable to a generic of compounds; which requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the compound or generic(s). For example, in a recent court case in line with *Eli Lilly, Judge Lourie writing for the CAFC* made the following observation:

"A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) having the function of lessening inflammation of tissues, fails to distinguish any steroid from others having the same activity or function. Similarly, the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity. "

See: J. Lourie decision in *Enzo Biochem, Inc. v. Gen-Probe Inc. et al.* No. 01-1230 (CAFC: Decided April 2, 2002) (citation forthcoming).

In this regard, applicant is further referred to the seminal case of *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and the "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001).

It is noted that written description is legally distinct from enablement: "Although the two concepts of are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures

the that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co.*

Accordingly, claiming "sublancin 168" and "sublancin" (as in claims 5 and 9, respectively) without reference to any amino acid structure whatsoever lacks adequate written description.

9. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the assay use of lantibiotic display peptides of defined sequence (e.g. sublancin); an amino acid spacer of defined length and composition; and a subtilin leader peptide comprising amino acid residues 78-81 of seq. Id 2, the specification does not reasonably provide enablement for the scope of the presently claimed assay use of lantibiotic display peptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims.

2. The nature of the invention

3. The state of the prior art;

4. The level of one of ordinary skill

5. The level of predictability in the art;

6. The amount of direction provided by the inventor;

7. The presence or absence of working examples;

8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure;

See :*In re Wands* USPQ 2d 1400 (CAFC 1988):

(1-2) The breadth of the claims and the nature of the invention:

The presently claimed invention is directed to methods of:

I. Detecting binding of a target molecule to a "Lantibody display Peptide" by reacting a "host cell" expressing the lantibody display peptide on its surface with the target molecule and measuring a change in biological activity of the target molecule (claim 1); or

II. Screening a "Lantibody display library" for binding to one or more target molecules by reacting a "plurality of bacterial cells" expressing different lantibody display peptides on their surfaces, with one or more target molecules and isolating bacterial cells binding a target molecule "using means for recognizing the binding agent" (claim 7).

The above methods employ the use of chimeric lantibiotic display peptides that comprise:

1. A "lantibiotic peptide" (see specification page 1 definition thereof);

2. An "amino acid spacer" attached to the C-terminus of the lantibiotic peptide; and

3. A "subtilin leader segment" attached to the spacer. See present claim 1.

Lantibodies bind "specifically to desired molecules" in the nature of antibodies (see specification pages 2-3).

Thus, the presently claimed invention is broadly directed to an "amino acid spacer" containing any amino acids and any length (e.g .no upper limit) and a "subtilin leader segment" and "lantibiotic peptide" of unnamed amino acid structure and/or length.

However, the specification further teaches that in order to obtain a functional lantibiotic display peptide:

I. The "subtilin leader segment" must be fused to the C-terminus of the lantibiotic peptide *via its N-terminus* (emphasis provided) in order to anchor the lantibiotic peptide to the cell surface of a host cell and avoid cleavage by a signal peptidase (e.g. see specification at pages 5 and 9.

II. The "subtilin leader segment" must at least comprise amino acid residues 78-81 of seq. Id 2 (e.g. see specification at pages 6-8: "residues 78-81 are necessary"); and

III. The "amino acid spacer" must comprise 1-40 non-polar amino acids in order to be of sufficient length and design to produce a region with unstructured secondary conformation (e.g. see specification on pages 6-8).

(3 and 5) *The state of the prior art and the level of predictability in the art:*

Lantibodies bind "specifically to desired molecules" in the nature of antibodies (see specification pages 2-3). Thus, in accordance with the present invention, the ability of a lantibiotic display peptide to predictably bind a receptor/target is a prerequisite for

obtaining "biological activity". However, ligand/receptor binding is stereospecific (e.g conformationally sensitive).(see Rudinger, Peptide Hormones (June 1976: J Parsons editor) pages 1-6; e.g. see page 4; and accordingly, the efficacy of binding of a ligand (e.g. cyclopentapeptide) to a receptor (e.g. enzyme/hormone etc.) to achieve physiological action is determined by the conformation of the given ligand. Thus the different aspects of biological activity cannot be predicted *a priori* but must be determined on a case to case base through experimental study. The careful design of synthetic analogues and their evaluation in biological systems which permit separate analysis of the various phases of receptor (e.g hormone) action is the best way of obtaining such information. See Rudinger, Peptide Hormones, (June 1976) (J.A. Parsons, editor) 1,5-6. Although the Rudinger article is directed to peptide ligands binding hormone receptors; the conformational sensitivity and unpredictability of binding attributed to peptide ligands is clearly extrapolatable to ligand/receptor interactions generally.

(4) *The level of one of ordinary skill in the art:*

The level of skill would be high, most likely at the Ph.D. level.

(6-7) *The amount of direction provided by the inventor and the existence of working examples.*

The specification examples are directed to the making or use of lantibiotic display peptides directed to a sublancin (as the "lantibiotic peptide") peptide comprising the amino acids residues 1-38 of Seq. Id. 2 attached (via its C-terminus) to polyglycine

linkers of defined length to which is attached to the subtilin leader peptide sequence (amino acids 58-81 of Seq. Id. 2) via its N-terminus.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

According to case law, method and compound parameter (s) which are established (e.g. by the specification and/or by the prior art) to be **essential or critical** to the practice of a claimed invention (compound or method), renders claims which lack such essential subject matter non-enabled. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976) (e.g. critical reaction parameters established in specification); and ***Ex Parte Bhide*** **(Bd Pat. App. & Int.) 42 USPQ2d 1441 (e.g. critical core structure established by publication(s) (emphasis provided).**

As discussed above, applicant's own specification discloses criticality regarding the length and composition of the amino acid linker; and regarding subtilin leader segments, the presence of critical amino acid residues and N-terminal attachment to the linker.

In view of the broad scope of lantiobiotic display peptides of the present claims; the unpredictability and expected inoperatability of claimed peptides lacking core peptide structure, linker length/composition ; the case law which requires critical parameters to be present in claims; it would necessarily result in undue experimentation by one of ordinary skill in the art wishing to practice applicant's invention for the full scope of lantibiotic display peptides; and additionally would be deemed nonenabled in accordance with existing caselaw.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

11. Claims 1-4 and 6 are rejected under 35 U.S.C. 102(a,b,e) as being anticipated by Hansen U. S. Pat. No. 5,516,682 (5/96) alone or further in view of the specification (e.g. at page 7) as evidence of inherency.

The presently claimed invention is directed to methods of:

I. Detecting binding of a target molecule to a "Lantibody display Peptide" by reacting a **"host cell"** expressing the lantibody display peptide on its surface with the target molecule and measuring a change in biological activity of the target molecule employing the use of chimeric lantibiotic display peptides that comprise:

1. A "lantibiotic peptide" (see specification page 1 definition thereof);

2. An "amino acid spacer" attached to the C-terminus of the lantibiotic peptide; and

3. A "subtilin leader segment" attached to the spacer.

The Hansen reference discloses and claims (e.g. see seq. Id 6 and 7) 56 amino acid subtilin mutant (derivable from *bacillus subtilis*: see e.g. patent claim 11) peptides that comprise:

1. A "lantibiotic peptide" e.g. subtilin or a portion thereof;

2. A "subtilin leader segment" comprising amino acid residues: 58-81; 68-81 and 78-81 of present seq. Id 2

with an amino acid spacer linking the subtilin peptide segment to any one of the above "subtilin leader segment(s)" with the spacer spanning up to 20 amino acids (e.g. 20 corresponding to leader segment 78-81). The reference amino acid spacer is attached to the C-terminal portion of the "lantibiotic peptide" and the N-terminal portion of the "subtilin leader segment" in accordance with the presently claimed invention.

With regard to the term "lantibiotic display" it is noted that the reference peptides ability to meet the presently claimed structural requirements ensures that the reference peptide inherently meets the functional requirements corresponding to the term "lantibiotic display". Additionally, it is noted that the reference peptides comprise sufficient subtilin leader sequence (e.g. comprise at least 78-81 of seq. Id 2) to impart "lantibiotic display" properties. See e.g. present specification at pages 6-8. The Hansen reference further teaches a biological assay (e.g. "spore outgrowth assay") directed to the binding of the lantibody display peptides to a "nucleophilic group of a target molecule" (e.g. spore) and measuring a change in a biological activity of the target

molecule (e.g. inhibition of growth/proliferation of the infectious spore. See col. 6-8). The term "chimeric" in the present claims could be deemed to be intended use or manufacture; and as such would not be afforded patentable weight in the present compound/composition claims. Alternatively to the extent that use of the term "chimeric" transforms present claim 1 into a product by process claim, it is noted that product by process claims are treated for purposes of patentability by the PTO as product claims and thus the reference making of polypeptides within the presently claimed scope, even by a different means (e.g other than chimeric) would still anticipate the presently claimed invention. Additionally, it is noted that the recombinant production of the mutant reference polypeptides would be within the scope of the term "chimera" as defined in the specification (e.g see pages 5-7) since the reference polypeptide is a fusion polypeptide comprised of two or more different peptide segments (some native, some non-native).

12. Claims 1-4 and 6 are rejected under 35 U.S.C. 102(a,b,e) as being anticipated by Hansen WO 97/11713 (4/97).

The presently claimed invention is directed to a method of:

Detecting binding of a target molecule to a "Lantibody display Peptide" by reacting a **"host cell"** expressing the lantibody display peptide on its surface with the target molecule and measuring a change in biological activity of the target molecule employing the use of chimeric lantibiotic display peptides that comprise:

1. A "lantibiotic peptide" (see specification page 1 definition thereof);

2. An "amino acid spacer" attached to the C-terminus of the lantibiotic peptide; and

3. A "subtilin leader segment" attached to the spacer.

The Hansen reference discloses and claims (e.g. see abstract; examples and claims 1-20) a polynucleic acid encoding a "chimeric" polypeptide comprising:

1. A "lantibiotic peptide" e.g. (mutants of)subtilin/ (mutants of) nisins/ or chimeras of subtilin and nisin (e.g. see claim 2);

2. A "subtilin leader segment" (e.g. a "chimeric leader: comprising subtilin/nisin leaders including NL-SL: i.e. see claim 4;

with an amino acid spacer linking the "lantibiotic" and "leader" sequences; and the reference amino acid spacer attached to the C-terminal portion of the "lantibiotic peptide" and the N-terminal portion of the reference "leader" sequence in accordance with the presently claimed invention. Particulary, the reference claim 1 and 4 (2^{nd} chimeric leader sequence) is clearly within the scope of the presently claimed invention.

With regard to the term "lantibiotic display" it is noted that the reference encoded chimeric peptide compound comprise peptidic structure within the scope and which are encoded in host cells within the scope of the presently claimed invention (e.g. bacillus subtillus 168: e.g. see page 11) presently claimed invention which ensures that the reference peptide inherently meets the functional requirements corresponding to the term "lantibiotic display". Additionally, it is noted that the reference peptides comprise sufficient subtilin leader sequence to impart "lantibiotic display" properties. See e.g. present specification at pages 6-8. The Hansen reference further teaches a biological assay (e.g. "spore outgrowth assay") directed to the binding of the lantibody display

peptide to a "nucleophilic group of a target molecule" (e.g. spore) and measuring a change in a biological activity of the target molecule (e.g. inhibition of growth/ proliferation of the infectious spore. See specification and examples.

Claim Rejections - 35 USC § 103

13. Claims 1-4 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen U. S. Pat. No. 5,516,682 (5/96) [with the specification to demonstrate inherency] or Hansen WO 97/11713 (4/97) and Gyuris et al. US Pat. No. 6,420,110 (7/02: filed 10/98).

The presently claimed invention is directed to methods of:

I. Detecting binding of a target molecule to a "Lantibody display Peptide" by reacting a "host cell" expressing the lantibody display peptide on its surface with the target molecule and measuring a change in biological activity of the target molecule (claim 1); or

II. Screening a "Lantibody display library" for binding to one or more target molecules by reacting a "plurality of bacterial cells" expressing different lantibody display peptides on their surfaces, with one or more target molecules and isolating bacterial cells binding a target molecule "using means for recognizing the binding agent" (claim 7).

The above methods employ the use of chimeric lantibiotic display peptides that comprise:

1. A "lantibiotic peptide" (see specification page 1 definition thereof);

2. An "amino acid spacer" attached to the C-terminus of the lantibiotic peptide; and

3. A "subtilin leader segment" attached to the spacer. See present claim 1. Lantibodies bind "specifically to desired molecules" in the nature of antibodies (see specification pages 2-3).

The Hansen '682 reference discloses and claims (e.g. see seq. Id 6 and 7) 56 amino acid subtilin mutant (derivable from *bacillus subtilis*: see e.g. patent claim 11) peptides that comprise:

1. A "lantibiotic peptide" e.g. subtilin or a portion thereof;

2. A "subtilin leader segment" comprising amino acid residues: 58-81; 68-81 and 78-81 of present seq. Id 2

with an amino acid spacer linking the subtilin peptide segment to any one of the above "subtilin leader segment(s)" with the spacer spanning up to 20 amino acids (e.g. 20 corresponding to leader segment 78-81). The reference amino acid spacer is attached to the C-terminal portion of the "lantibiotic peptide" and the N-terminal portion of the "subtilin leader segment" in accordance with the presently claimed invention.

With regard to the term "lantibiotic display" it is noted that the '682 reference peptides ability to meet the presently claimed structural requirements ensures that the reference peptide inherently meets the functional requirements corresponding to the term "lantibiotic display". Additionally, it is noted that the reference peptides comprise sufficient subtilin leader sequence (e.g. comprise at least 78-81 of seq. Id 2) to impart "lantibiotic display" properties. See e.g. present specification at page 7. The Hansen reference further a biological assay (e.g. "spore outgrowth assay") directed to the binding of the lantibody display peptide to a "nucleophilic group of a target molecule"

(e.g. spore) and measuring a change in a biological activity of the target molecule (e.g. inhibition of growth/proliferation of the infectious spore. See col. 6-8. The term "chimeric" in the present claims could be deemed to be intended use or manufacture; and as such would not be afforded patentable weight in the present compound/composition claims. Alternatively to the extent that use of the term "chimeric" transforms present claim 1 into a product by process claim, it is noted that product by process claims are treated for purposes of patentability by the PTO as product claims and thus the reference making of polypeptides within the presently claimed scope, even by a different means (e.g other than chimeric) would still anticipate the presently claimed invention. Additionally, it is noted that the recombinant production of the mutant reference polypeptides would be within the scope of the term "chimera" as defined in the specification (e.g see page 6) since the reference polypeptide is a fusion polypeptide comprised of two or more different peptide segments (some native, some non-native).

Similarly, The Hansen WO 97/11713 reference discloses and claims (e.g. see abstract; examples and claims 1-20) a polynucleic acid encoding a "chimeric" polypeptide comprising:

1. A "lantibiotic peptide" e.g. (mutants of)subtilin/ (mutants of) nisins/ or chimeras of subtilin and nisin (e.g. see claim 2);

2. A "subtilin leader segment" (e.g. a "chimeric leader: comprising subtilin/nisin leaders including NL-SL: i.e. see claim 4;

with an amino acid spacer linking the "lantibiotic" and "leader" sequences; and the reference amino acid spacer attached to the C-terminal portion of the "lantibiotic

peptide" and the N-terminal portion of the reference "leader" sequence in accordance with the presently claimed invention. Particulary, the Hansen WO reference claim 1 and 4 (2nd chimeric leader sequence) is clearly within the scope of the presently claimed invention.

With regard to the term "lantibiotic display" it is noted that the Hansen WO reference encoded chimeric peptide compound comprise peptidic structure within the scope and which are encoded in host cells within the scope of the presently claimed invention (e.g. bacillus subtillus 168: e.g. see page 11) presently claimed invention which ensures that the reference peptide inherently meets the functional requirements corresponding to the term "lantibiotic display". Additionally, it is noted that the reference peptides comprise sufficient subtilin leader sequence to impart "lantibiotic display" properties. See e.g. present specification at page 7. The Hansen reference further teaches a biological assay (e.g. "spore outgrowth assay") directed to the binding of the lantibody display peptide to a "nucleophilic group of a target molecule" (e.g. spore) and measuring a change in a biological activity of the target molecule (e.g. inhibition of growth/proliferation of the infectious spore. See specification and examples.

The above Hansen reference methods (e.g. '682 and WO) differ from the presently claimed invention (e.g. claims 7-8) by failing to teach high throughput screening of Lantibody display peptide libraries (e.g. 2 or more bacteria cells expressing different lantibody display peptides on their surface) for "target" binding and isolating the bacterial cells for "recognizing the binding agent").

However, Gyuris et al. teach that "high throughput screening has become a dominant tool in the pharmaceutical industry for the discovery of lead compounds that can be modified into candidates for drug development" e.g. by identifying ligands with high affinity for receptors (e.g. enzymes, antibodies etc.: e.g. see col. 1, lines 15-37; col. 22-23, especially lines 29-67 for antibodies and enzymes) which involves selection and amplification of a subset of molecules with desired biological properties. E.g. see col 1, especially lines 5-15. Accordingly, Gyuris teaches isolating peptides having a desired biological activity (e.g. ligands which bind targets affecting biological activity of targets) which includes "variegated peptide display" (e.g. different peptides as part of library: see abstract; col. 30 definition) utilizing chimeric genes expressing fusion peptides and the surface protein (including peptide linkers: see col. 10-11), including bacterial cell surface and spore display libraries, utilizing host cells including *bacillus subtillus.* The library peptide ligands may bind to a diverse number of targets including enzymes (E.g. GTPase, phospholipase) and change the biological activity of the target (e.g. enzyme phosphorylation); with isolation of the bacterial cells comprising target-binding ligands. See e.g. col. 1-4; col. 5 (especially lines 20-40); col. 6 (especially lines 37-65); col. 17-23; col. 26; col. 33-37; patent claims 1-42 (especially claims 1, 6, 12-42).

The Gyuris et al. reference provides motivation to one of ordinary skill in the art at the time of applicant's invention to utilize variegated bacterial (e.g. *bacillus subtillus)* cell-surface display utilizing the Hansen WO 97/11713 (4/97) or Gyuris et al. US Pat. No. 6,420,110 chimeric polypeptides comprising lantibiotics-subtilin leader segments in order to take advantage of high throughput screening which has become a dominant

tool in the pharmaceutical industry for the discovery of lead compounds that can be modified into candidates for drug development" e.g. by identifying ligands with high affinity for receptors which involves selection and amplificataion of a subset of molecules with desired biological properties. One would have a reasonable expectation of success in utilizing high throughput variegated bacterial cell surface as disclosed by Gyuris since Gyuris teaches employing "chimeric" polypeptides and bacterial host cells (e.g. . *bacillus subtillus)* as employed in the Hansen reference teachings.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention *to employ in the* above Hansen reference methods high throughput screening of Lantibody display peptide libraries (e.g. 2 or bacteria cells expressing different lantibody display peptides on their surface) for "target" (e.g. enzyme) binding and isolating the bacterial cells for "recognizing the binding agent") in accordance with the teaching of the Gyuris method.

Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
October 27, 2004